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Biological Psychiatry: Celebrating 50 Years

Strengthened Hippocampal Circuits Underlie Enhanced Retrieval of Extinguished Fear Memories Following Mindfulness Training

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ABSTRACT

BACKGROUND: The role of hippocampus in context-dependent recall of extinction is well recognized. However, little is known about how intervention-induced changes in hippocampal networks relate to improvements in extinction learning. In this study, we hypothesized that mindfulness training creates an optimal exposure condition by heightening attention and awareness of present moment sensory experience, leading to enhanced extinction learning, improved emotion regulation, and reduced anxiety symptoms.

METHODS: We tested this hypothesis in a randomized controlled longitudinal study design using a 2-day fear conditioning and extinction protocol. The mindfulness training group included 42 participants (28 women) and the control group included 25 participants (15 women).

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CONCLUSIONS: These findings suggest hippocampal-dependent changes in contextual retrieval as one plausible neural mechanism through which mindfulness-based interventions enhance fear extinction and foster stress resilience.

Keywords: Extinction, Extinction retrieval, Fear memory, fMRI, Hippocampus, Mindfulness

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The ability to recall that a stimulus is no longer associated with threat is crucial to healthy emotional functioning and is a major component of emotion regulation (1–3). This ability serves as the basis for exposure-based therapies and is critical to treat a variety of disorders including phobia, trauma, and other anxiety disorders (4,5). During exposure-based therapies, individuals are presented with fear-inducing stimuli in a controlled environment until the response to the eliciting stimulus gradually declines while behavioral patterns of avoidance that reinforce the fear response dissolve (6). Mindfulness meditation is thought to create a state of optimal exposure (7,8) in which aversive stimuli are experienced with nonreactive acceptance (7,8), and facilitate extinction learning. Mindfulness-enhanced extinction learning and the neural mechanisms associated with this enhancement, however, have not been fully explored.

Extinction learning entails the formation of a new association and consists of separate processes of acquisition, consolidation, and retrieval (9–11). The hippocampus is critical to the consolidation and retrieval processes and gates the expression of either the conditioned fear or extinction memory, depending on contextual information (12–15). Mindfulness training leads to improvements in memory (16,17) as well as to changes in hippocampal structure and function (18–20). Relying on the critical role of the hippocampus in context-dependent retrieval of extinguished stimuli and the conceptual similarity between therapeutic exposure and mindful awareness, we hypothesize that mindfulness training might lead to improvements in extinction learning through alterations in hippocampal functioning during retrieval. Furthermore, core components of mindfulness training include attention control, emotion regulation, and sensory awareness (21). Investigations into the effects of mindfulness interventions on a range of health outcomes have also identified alterations in somatosensory processing (22,23) and attentional networks as mediators of these improvements (24,25). Given the role of attention in retrieval, and the critical role of corticohippocampal networks, we hypothesize that training-dependent changes in these networks might also contribute to changes in extinction learning and retrieval.

We tested these hypotheses in a randomized, controlled study using a well-established fear conditioning and extinction paradigm adapted for the magnetic resonance imaging (MRI) environment before and after an 8-week mindfulness-based stress reduction (MBSR) or exercise-based stress management education (SME) program (1,13,26). This active control condition was matched to MBSR in the amount of facilitator

SEE COMMENTARY ON PAGE 652

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contact and home practice assigned to allow for an examination of mechanisms of action specific to mindfulness training. Importantly, because exercise is well known to promote emotion regulation (27), as well as enhance hippocampal structure and function (27,28), we expected comparable increases in functional engagement of the hippocampus for both interventions. However, assuming different mechanisms of action, we hypothesized that mindfulness training would differentially impact the functional connectivity of hippocampal networks, predominantly in regions associated with attention, sensory awareness, and contextual processing.

METHODS AND MATERIALS

Participants

Subjects 18 to 50 years of age were recruited via public transportation advertisements for stress-reduction programs. In addition to the standard MRI safety exclusion criteria, participants were required to be right-handed, have no current psychiatric or neurological disorders, and not be engaged in psychotherapy or have taken psychotropic medications within 12 months prior to the study. They were required to have had minimal prior experience with meditation or yoga practice, as defined by having taken no more than 4 meditation classes of any kind in the past 12 months, or more than 10 classes in their lifetime. Participants were remunerated up to \$100 for participation.

Participants were randomized to 1 of 2 stress reduction programs, MBSR or SME on a 2:1 ratio, stratified by gender. This ratio was chosen to maximize power for correlational analyses in the MBSR group. In total, 94 participants completed initial testing and were randomized; 89 attended at least 1 class (58 MBSR, 31 SME), and 49 MBSR and 27 SME participants completed MRI scanning at the post time point. The Partners HealthCare Institutional Review Board approved the study protocol; all participants provided written informed consent. There were no differences between groups in terms of gender (MBSR: 28 women, 14 men; SME: 15 women, 10 men [$\chi^2_1 = 0.30$, $p = .58$]), age (MBSR 31.14 $\pm$ 7.71 years; SME 33.08 $\pm$ 18.02 years [$t_{65} = -0.94$, $p = .35$]), or years of education (MBSR 17.40 $\pm$ 3.08 years, SME 18.02 $\pm$ 2.51 years [$t_{65} = -0.84$, $p = .40$]). The minimum number of participants who fully completed self-report measures was 37 for MBSR and 22 for SME. The number of participants who had functional neuroimaging data available at day 2 was 42 for MBSR and 25 for SME. The total hours of home practice was 23.50 $\pm$ 10.87 hours for MBSR and 34.82 $\pm$ 19.74 hours for SME.

Questionnaires

Questionnaires included the Perceived Stress Scale (PSS) (29), Spielberger State–Trait Anxiety Inventory (30), the Difficulties in Emotion Regulation Scale (DERS) (31), and the Mindful Attention Awareness Scale (32). Repeated-measures t tests and analyses of covariance were used to determine statistically significant differences within and between the groups on the behavioral outcome measures using SPSS version 24 (IBM Corp., Armonk, NY). From the MBSR group, 37 completed the Perceived Stress Scale, State–Trait Anxiety Inventory, and Mindful Attention Awareness Scale questionnaires, and 39 completed the DERS questionnaire; from the SME group these numbers were 22 and 23 participants, respectively.

Fear Conditioning and Extinction Paradigm

The scanning protocol comprised a 2-day classical fear conditioning and extinction paradigm validated in healthy subject (4,33) and patient (1,2,34) populations. Briefly, the fear-conditioning procedure consisted of acquisition ("conditioning") and extinction phases on day 1, and a delayed extinction recall phase on day 2. Skin conductance responses were collected and scored as previously described (2,13) (see the Supplement). Owing to low data quality and low compliance with our criteria (i.e., to exhibit signal changes during conditioning), only16 participants had both functional neuroimaging and skin conductance data (8 per group).

Image Acquisition

Imaging data were acquired on a Siemen's Prisma 3.0T equipped for echo-planar imaging (Siemens Medical Systems, Iselin, NJ) with a 32-channel gradient head coil. An automated scout image was obtained to facilitate alignment of pre- and postintervention scans. High-resolution 3-dimensional magnetization prepared rapid acquisition gradient-echo sequences were acquired (repetition time/echo time/flip angle = 2.53 ms/1.74 ms/7 degrees; 1-mm isotropic voxels; field of view = 256 cm; 176 axial slices). Functional images were acquired with gradient-echo T2*-weighted sequences (repetition time/echo time/flip angle = 3 seconds/30 ms/90 degrees; field of view = 1400 $\times$ 1400; slice thickness = 2.5 isotropic voxels).

Functional MRI Data Analysis

All participants (n = 76) were scanned within 2 weeks before and after the courses. Data from 9 participants were unusable owing to technical problems during scanning (n = 2) or clerical errors (n = 7). Usable data were available for 42 MBSR and 25 SME participants. Functional data were analyzed using SPM12 (Wellcome Department of Neurology, London, United Kingdom), using standard preprocessing pipeline (see the Supplement). Both whole-brain and a priori region-of-interest (ROI) analyses were conducted. Neural activations within the hippocampi were examined using atlas-based anatomical ROIs (Neuromorphometrics atlas in SPM12). Similar to Milad *et al.* (13), additional correlation analyses were conducted to examine the relationship between the fMRI blood oxygen level–dependent (BOLD) signal changes in the hippocampus during extinction recall and the magnitude of the psychophysiological index of extinction memory recall at baseline. For the correlation between index of extinction memory and neural signal estimates, we used peak coordinates previously reported in Milad *et al.* (13) and extracted signal values from this ROI using MarsBaR (35) using a sphere with a radius of 6 mm, and using the extinguished stimuli (CS+E) in reference to baseline fixation contrast. This ROI will be referred as functional ROI, while atlas-based ROIs will be referred as anatomical ROIs. To assess differences between groups in terms of β estimates within the a priori functional ROI, an analysis of variance was used. For the event-related analysis, a trial averaging window of 21 seconds beginning 6 seconds prior to the trial onset was used. The contrast of interest at the first level was CS+E versus conditioned stimulus never paired with the shock (CS–) and allowed us to assess neural responses that were specific for extinction recall. These first-level analyses were subjected to a second-level analysis using a fully flexible factorial design with the following factors: subject, time (pre and post), and group (MBSR and SME). Task-related responses were considered to be significant at a threshold of $p < .001$ at the voxel level and at a threshold of $p < .05$ using familywise error (FWE) correction at the cluster level. β estimates from the peak were then extracted to interpret the interaction effect.

For analysis of functional connectivity, we performed seed-based connectivity analysis using the weighted general linear modeling option in the CONN toolbox (36) (see the Supplement for details). The seed was an anatomical ROI of the entire left hippocampus, based on the parcellation scheme of the Harvard-Oxford Atlas. The results reflect connectivity of the ROI to the whole brain. For reconstruction and segmentation of the brain, FreeSurfer image analysis suite version 5.3 was used following the longitudinal analysis stream (37–39). For the analyses of the relationship between structure and function, symmetrized percent change in gray matter intensity was used (38) (see the Supplement for details). Studies of patient populations (2) and rodents (4) have demonstrated that a subset of functional alterations in neural processes related to the gating of the conditioned or extinguished memory were more robust during the early phases of extinction recall. Furthermore, it has been hypothesized that additional extinction learning may take place during the retrieval phase, which can potentially confound neural activity associated with extinction recall in later phases (2). Thus, all analyses were performed twice, first using all extinction recall trials, and then using only the first 4 CS+E extinction recall trials.

RESULTS

Mindfulness Training Leads to Improvements in Anxiety and Emotion Regulation

As expected, both MBSR and SME decreased levels of perceived stress (MBSR [n = 37]: ΔPSS = 4.57 $\pm$ 8.04 [t_{36} = 3.45, $p < .001$, Cohen's d = 0.56 (95% confidence interval, 1.89–7.25)]; SME [n = 22]: ΔPSS = 3.68 $\pm$ 6.52 [t_{21} = 2.65, p = .015, Cohen's d = 0.57 (95% confidence interval, 0.79–6.57)]), with no statistical difference between groups in ΔPSS scores (t_{59} = $-$0.44, p = .66) (Figure 1C). Three 1-way analyses of covariance were conducted to compare levels of mindfulness, anxiety, and emotion regulation at post while controlling for baseline levels. Levene's test and normality checks were carried out and the assumptions were met for the Mindful Attention Awareness Scale and State–Trait Anxiety Inventory. The

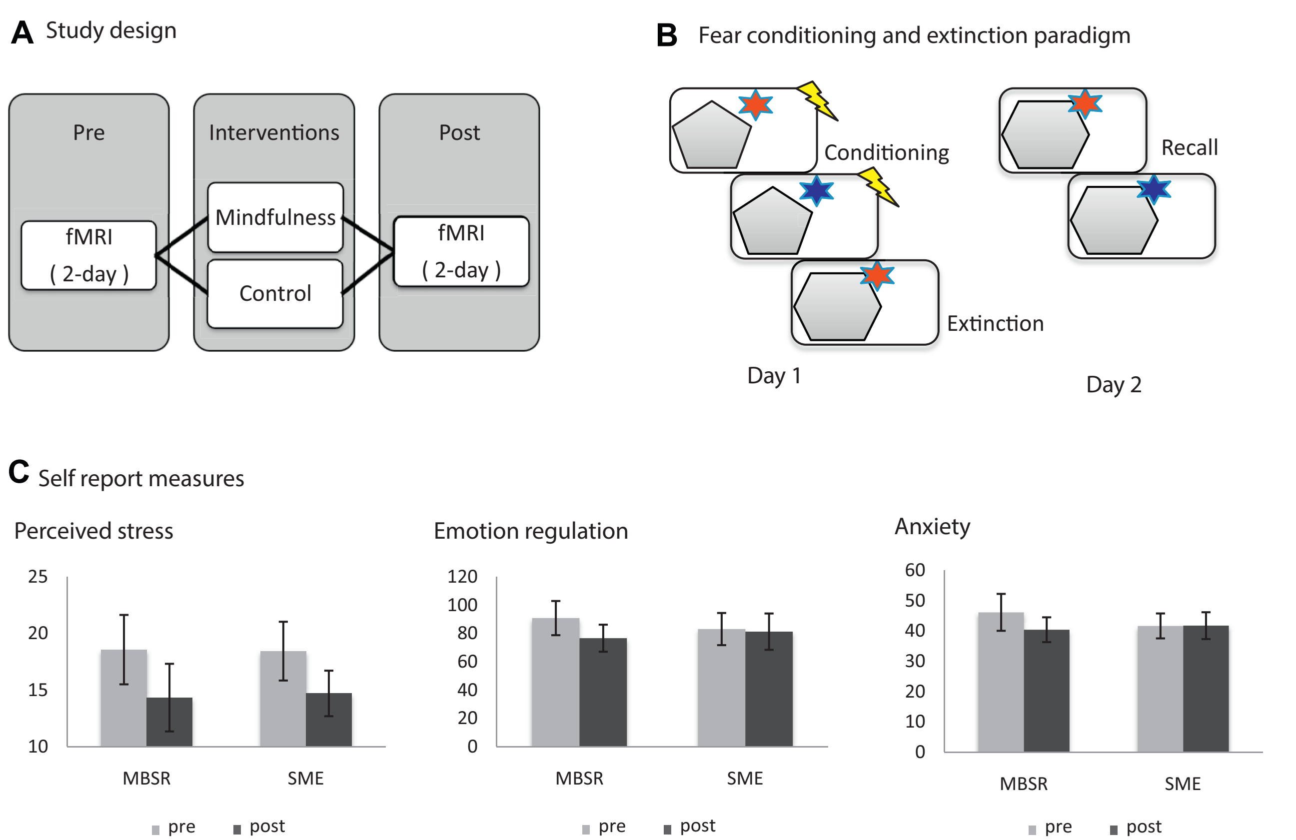

Figure 1. **(A)** Study design, **(B)** fear conditioning and extinction paradigm, and **(C)** changes in outcome measures. Error bars reflect standard deviations. Both interventions decreased perceived levels of stress; however, mindfulness-based stress reduction (MBSR) was associated with further improvements in anxiety and emotion regulation levels. fMRI, functional magnetic resonance imaging; SME, stress management education.

results suggested that there was a marginally significant difference in anxiety scores between the 2 groups at post ($F_{1,59}$ = 3.93, p = .052, partial η^2 = .63). For the DERS, a Shapiro-Wilk test of standardized residuals suggested a non-normal distribution at p = .37. A replication of 1-way analyses of covariance with log-transformed DERS scores suggested no statistically significant differences between the 2 groups ($F_{1,59}$ = 1.391, p = .243, partial η^2 = .23). There were also no differences between the MBSR and SME groups in terms of mindfulness levels ($F_{1,59}$ = 3.251, p = .77, partial η^2 = .55).

Hippocampal Activity During Recall at Baseline

We examined BOLD signal in both hippocampi using an atlas-based ROI during extinction recall for all subjects at baseline. A significant cluster in the left hippocampus was identified (cluster size [k = 19, 152 mm^3]), peak Montreal Neurological Institute (MNI) coordinates (−18, −30, −8) (FWE p = .015) (Figure 2A). A significant positive correlation was found between the extinction retention index (ERI) values and baseline hippocampal activity using parameter estimates extracted from this functional ROI with the peak voxel reported by Milad *et al.* (13), which reflects the ability to remember that a stimulus is no longer associated with threat (Pearson's r = .79, $p < .001$, n = 16) (Figure 2B). Stronger BOLD signals in the hippocampus were associated with larger ERI values.

Hippocampal Structural and Functional Changes During Recall Following the Interventions

There were no statistical differences between the 2 groups in terms of changes in ERI (MBSR: ΔERI = 0.68 ± 30.50; SME: ΔERI = 26.81 ± 51.2) (t_{14} = 1.24, p = .24). An independent-samples t test using symmetrized percent change values revealed no significant changes in the left hippocampal intensity between the MBSR (0.157 ± 1.09) and the SME (0.055 ± 1.20) (t_{59} = −0.962, p = .34) groups. BOLD signal contrast estimates from the left hippocampus were extracted using the a priori functional ROI. A repeated-measures analysis of variance revealed a significant main effect of time (Figure 2C) ($F_{1,65}$ = 14.423, $p < .001$), but no group-by-time interaction ($F_{1,65}$ = 1.063, p = .306). An exploratory analysis for within-group differences using a paired-samples t test demonstrated a significant increase for the MBSR group (t_{41} = 4.765, p = .000) and a nonsignificant increase for the SME group (t_{24} = 1.411, p = .171).

Mindfulness Training Enhances Activity in Supramarginal Gyrus During Extinction Recall

A whole-brain group-by-time analysis of BOLD signal during recall of extinguished stimuli using the CS+E versus CS– contrast identified differential engagement of a cluster in the right supramarginal gyrus (rSMG) (Figure 3A) (MNI coordinates [56, −40, 24]; Brodmann area 40; FWE p = .026). Investigation of the contrast estimates for each group at each time point indicated a larger increase for the MBSR group (n = 42) compared with the SME group (n = 25) from pre- to post-intervention (Figure 3B). Postintervention β estimates from this cluster significantly correlated with the total number of minutes of reported mindfulness practice at home for the MBSR group (r_{39} = .378, p = .018) (Figure 3C).

Mindfulness Training Increases Functional Coupling of the Hippocampus to Sensory Cortex During Extinction Recall

To test our hypothesis that MBSR and SME lead to differential changes in hippocampal functional coupling, we performed a group-by-time whole-brain analysis using an atlas-based left hippocampus seed. This analysis did not yield any significant results (FWE $p > .05$). However, a within-group analysis demonstrated that MBSR (n = 42), but not SME (n = 25), resulted in an enhanced functional coupling between the hippocampus and right primary sensory cortex (Figure 3D) (MNI coordinates [52, −28, 56]; k = 139; FWE p = .027). This region of the sensory cortex is typically associated with the left hand (40) and is consistent with placement of the shock electrodes in the present study.

Secondary whole-brain analysis using the initial 4 trials of extinction recall and an atlas-based left hippocampus seed identified a significant increase in the functional connectivity

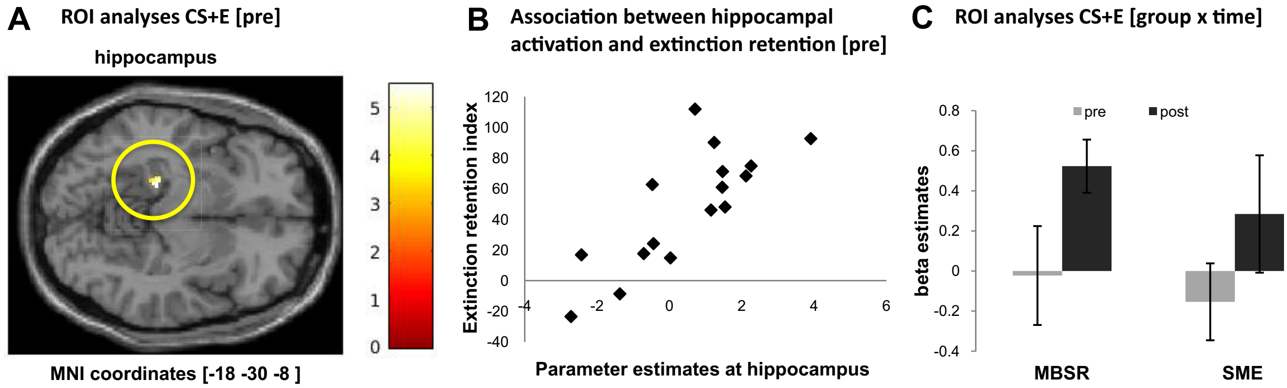

Figure 2. **(A)** Region-of-interest (ROI) analyses showing blood oxygen level–dependent (BOLD) signal in the hippocampus (left) during recall of extinguished stimuli for all participants at baseline. **(B)** Regression plot showing a positive correlation between the extinction retention index and parameter estimates extracted from the hippocampus [using peak from Milad *et al.* (13)]. **(C)** Parameter estimates extracted from second-level 1-sample t tests for each group and condition using the extinguished vs. conditioned stimulus never paired with the shock (CS+E vs. CS–) contrasts. Error bars reflect standard errors. MBSR, mindfulness-based stress reduction; MNI, Montreal Neurological Institute; SME, stress management education.

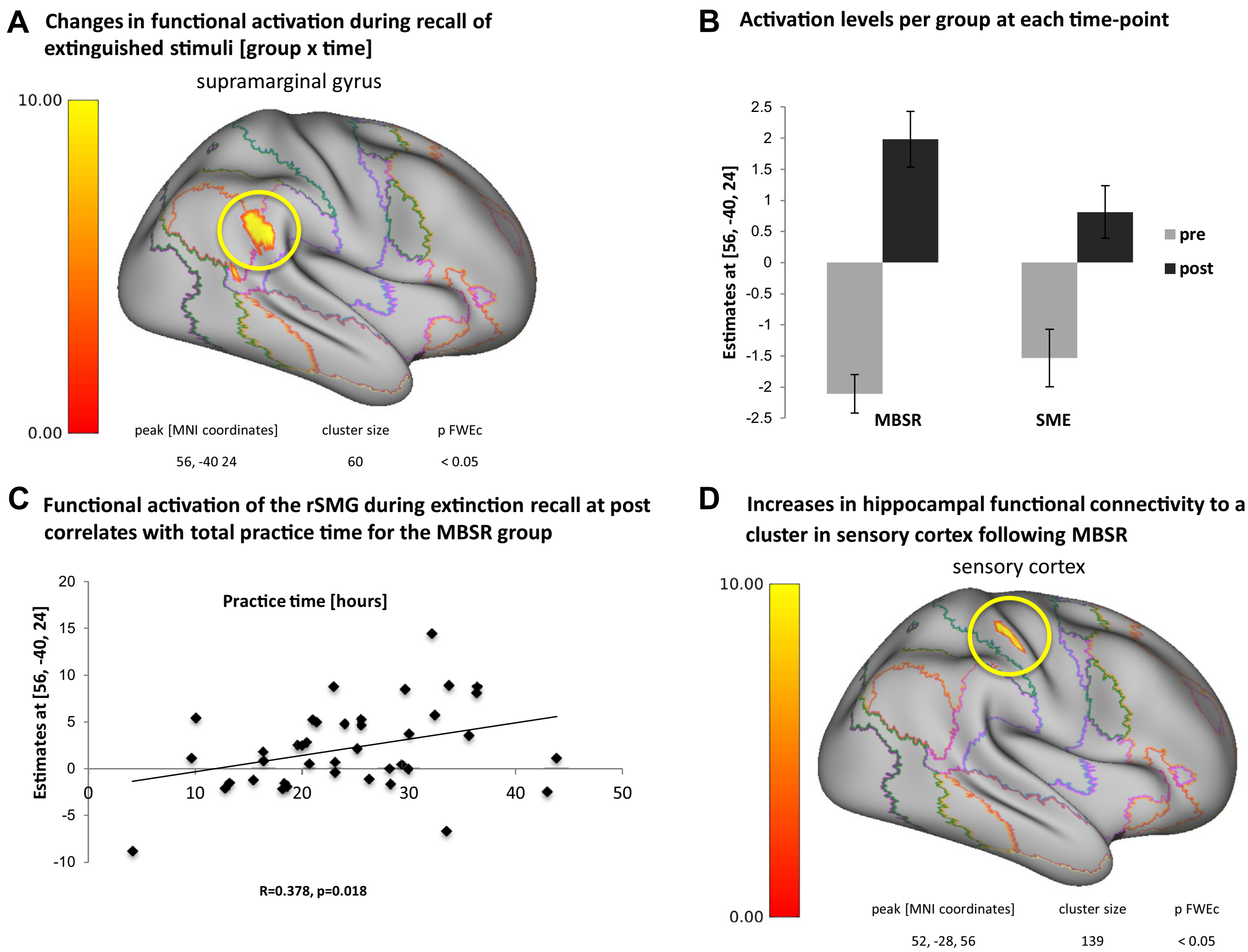

Figure 3. **(A)** The results of group-by-time analysis mapped onto Conte69 atlas via Connectome Workbench using trilinear interpolation. **(B)** Parameter estimates extracted from the peak [56, −40, 24], Brodmann area 40, using second-level 1-sample *t* tests for each group and condition using the extinguished vs. conditioned stimulus never paired with the shock (CS+E vs. CS–) contrasts. Compared with the control intervention, the mindfulness-based stress reduction (MBSR) intervention was associated with the higher engagement of a cluster in the right supramarginal gyrus (rSMG)/posterior parietal cortex. **(C)** Neural activity (parameter estimates of blood oxygen level–dependent signal extracted from the peak following MBSR intervention) correlate with total amount of home meditation practice during the MBSR intervention. **(D)** Changes in hippocampal functional connectivity during extinction recall following MBSR. FWEc, cluster level familywise error; MNI, Montreal Neurological Institute; rSMG, right supramarginal gyrus.

between the left hippocampus and a cluster in the rSMG for the mindfulness group from pre to post (n = 42; MNI coordinates [44, −30, 38]; k = 121; p = 0.002 uncorrected, false discovery rate p = .030). No significant relationships were observed for the SME group or the between-groups analysis (all FWE p values, $p > .05$).

Structural Changes in the Hippocampus Predict Enhanced Connectivity Between the Hippocampus and Contextual Cuing Regions During Early Phases of Recall

We have previously demonstrated mindfulness-training related increases in hippocampal gray matter density (41), which we speculated may be due in part to synaptogenesis (42). Therefore, we examined the relationship between change in hippocampal functional connectivity during extinction recall and symmetrized percent change in hippocampal gray matter intensity following both interventions. No significant relationships were found when examining alterations within the left hippocampus. Again, we repeated this analysis using the early phase of recall. Change in pre– to post–mean hippocampal gray matter was associated with enhanced connectivity between the hippocampus and left dorsolateral prefrontal (Figure 4) (MNI coordinates [−36, 54, 22]; k = 166; FWE p = .013) and retrosplenial (Figure 4) (MNI coordinates [22, −66, 14]; k = 126; FWE p = .046) cortices following mindfulness training.

DISCUSSION

Adaptively responding to threat signals and updating the meaning of those signals as they change is critical for mental health. A failure to update stimulus-response associations has

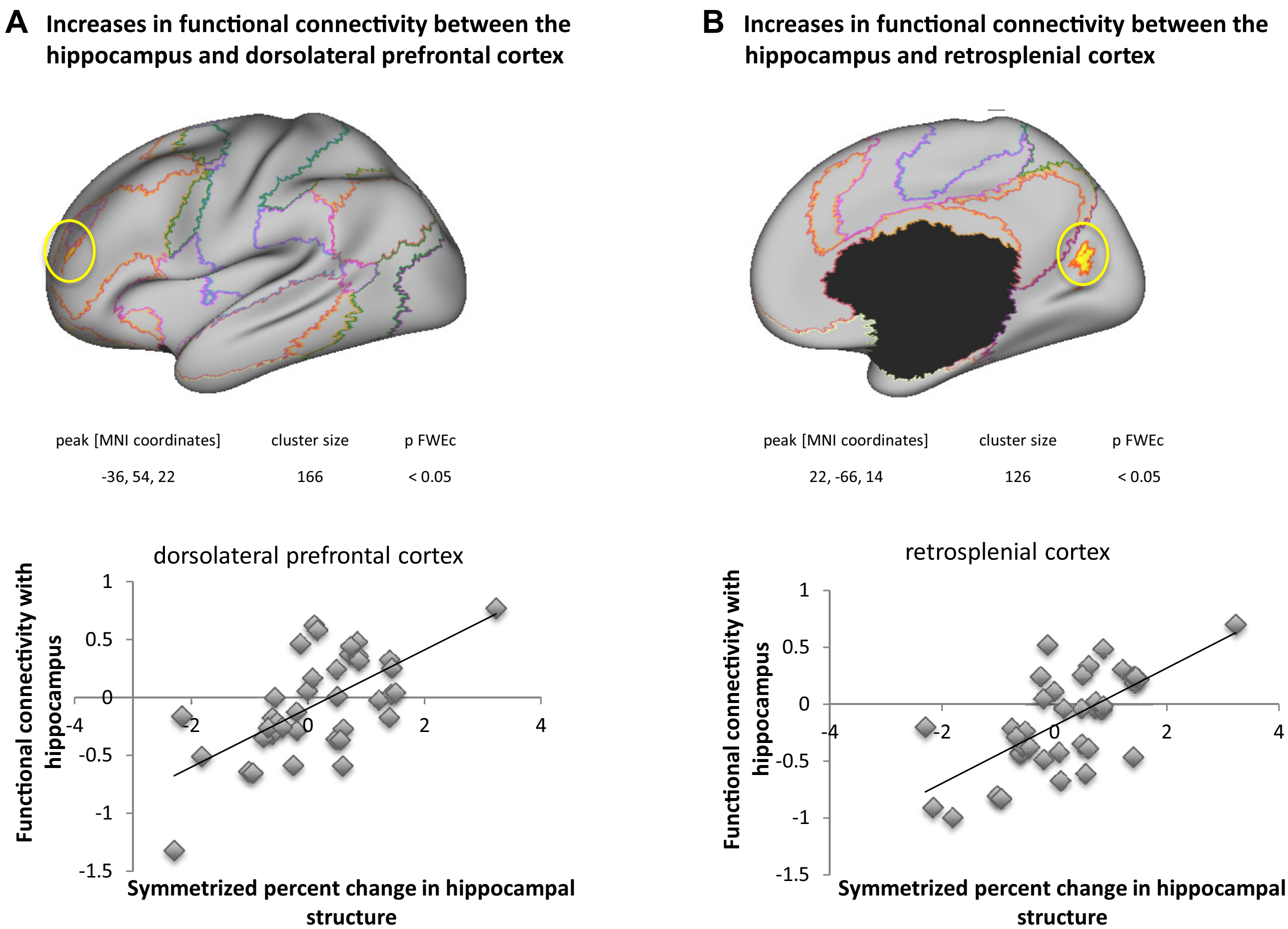

Figure 4. Structural change in the hippocampus from pre to post predict increased functional connectivity between the hippocampus and dorsolateral prefrontal **(A)** and retrosplenial **(B)** cortices during the early phases of recall at post for the mindfulness-based stress reduction group. The graphs show connectivity values between the hippocampus and the dorsolateral prefrontal **(A)** and retrosplenial **(B)** cortices as they covary with symmetrized percent change in hippocampal signal intensity. The x-axis depicts symmetrized percent change in hippocampal signal intensity, while the y-axis depicts the Fisher-transformed correlation coefficient of connectivity between the hippocampus and the relevant cluster. FWEc, cluster level familywise error; MNI, Montreal Neurological Institute.

been implicated in the pathophysiology of several anxiety disorders (43,44). Yet, ways to enhance the capacity to update those associations and, more importantly, to retain and retrieve these newly formed adaptive representations remain largely unknown. Relying on the role of the hippocampus in retrieval of contextual information to signal safety (5), we postulated that mindfulness training would promote changes in the hippocampus and thereby enhance extinction memory retrieval. An investigation of functional activity during extinction recall demonstrated differential engagement of the supramarginal gyrus following mindfulness training as well as increased connectivity between the hippocampus and the supramarginal gyrus during the early phase of extinction recall for the mindfulness group. Providing further evidence for the neuroadaptive changes associated with mindfulness training, we found increased connectivity between the hippocampus and primary somatosensory cortex, specifically in the area of the primary somatosensory cortex that corresponds to where the shock electrodes had been placed. These findings suggest that strengthened hippocampal circuits following mindfulness training are associated with enhanced retrieval of extinguished fear memories and advocate extinction learning as a mechanism through which mindfulness training may foster resilience and reduce stress and anxiety.

Longitudinal changes in hippocampal structure and function have long been thought to be key components in the development of stress resilience following mindfulness training (21,45). Changes in hippocampal structure and function have also been reported following aerobic and strength training (27,46). By comparing mindfulness training with an active control that included exercise, we aimed to isolate the specific effects of mindfulness training on hippocampal function. While functional changes within the hippocampus were not specific to mindfulness training, and the changes in functional activation and connectivity did not survive between group analyses, only mindfulness training enhanced connectivity between the hippocampus and a primary sensory cortex cluster where participants had received the shock (i.e., the unconditioned stimulus). This finding is in line with previously reported increased sensory processing following mindfulness training

(23) and may reflect mindfulness training's strong emphasis on heightened awareness of somatosensory information.

We previously demonstrated mindfulness training–dependent influences on fear acquisition in a small pilot study (47). Specifically, compared with a waitlist group, the mindfulness training group exhibited no change in conditioning from pre to post while the waitlist group exhibited decreased conditioning. This differential conditioning was correlated both with decreases in perceived stress and with a significant increase in fractional anisotropy in the right uncinate fasciculus. Although counterintuitive, this finding is consistent with mindfulness instructions to bring attention to present moment sensory experience with an accepting and nonjudging attitude (48). The finding is also consistent with previous studies with experienced meditation practitioners that have demonstrated enhanced neural signal in both primary and secondary sensory cortices during experimentally induced pain (22,49), as well as decoupling between sensory regions and frontal executive regions (50). In line with these prior studies, we interpret our current finding of enhanced hippocampal–primary somatosensory cortex coupling during recall to indicate improved contextual retrieval of sensory experience associated with extinguished stimuli. This finding implies that mindfulness practice likely altered the conditioning as well as the extinction processes. We will report the analysis of those conditions elsewhere. All in all, the current results are consistent with previous findings that one's ability to pay attention to sensory experience is a critical component of extinction learning in therapeutic settings (50).

Mindfulness training programs emphasize the development of focused attention and have been previously associated with significant improvements in selective and executive attention (51). In line with the pivotal role of attention in retrieval (52), we observed enhanced activation in the rSMG. The rSMG has been implicated in memory retrieval, specifically in directing the attentional capture to task-relevant memory contents and matching them with the current retrieval cue (53). This region has been proposed to shift attention to, or maintain attention on, internally generated mnemonic representations and direct voluntary attention to memory contents, depending on task demands (54,55). It is also part of the ventral frontoparietal system that is thought to be involved in detecting unattended or unexpected stimuli and triggering shifts of attention in a bottom-up fashion (56). Accordingly, enhanced rSMG engagement during retrieval, together with increased coupling between the hippocampus during the early phase of retrieval, may imply differential influence of mindfulness training on attentional regulation to promote context-based extinction recall. This interpretation is supported by the extensive anatomical connectivity between the posterior parietal cortex and the medial temporal lobe regions specifically involved in retrieval (57), previous reports of SMG activation during the retrieval of extinguished stimuli (13), and our observed correlation between rSMG activation following mindfulness training and reported practice time. The cross-hemisphere interaction between the left hippocampus and rSMG is also in line with left-lateralized retrieval–related medial temporal lobe activations (53,58) and right-lateralized perceptual attention–related posterior parietal cortex activations (59). Together, these findings highlight the significance of attentional processes during extinction learning and suggest a mechanism through which mindfulness training may differentially contribute to improvements in extinction recall.

In line with the plausible association between brain structure and function, increases in hippocampal gray matter intensity following mindfulness training predicted enhanced connectivity between the hippocampus and the dorsolateral prefrontal cortex (DLPFC) and retrosplenial cortex. Both regions have previously been shown to play a role in the recall of fear extinction (60,61). DLPFC activation during extinction recall has specifically been associated with reappraisal (62), the manipulation or reinterpretation of the meaning of a conditioned stimulus (15), and exposure therapy (50). Importantly, one the one hand, increased connectivity within a DLPFC-cingulate-parietal-hippocampal network has been associated with suppression of previously encoded associations (63), which is important for preventing memories of the conditioned stimulus from interfering with the extinction memory. The retrosplenial cortex, on the other hand, is structurally connected to parahippocampal areas (57) and has also been implicated in episodic memory (60,64). Critically, the degree of connectivity between the retrosplenial cortex and other areas in the fear network has been associated with the degree of contextual memory retrieval (65). Improvements in the intrinsic connectivity of the retrosplenial cortex have been previously reported following mindfulness training as well (66). Given that the retrosplenial cortex can bridge the medial temporal lobe and cortical default mode network regions that underlie contextual processing during episodic memory, we postulate that mindfulness-dependent increases in hippocampal structure may underlie changes in context-dependent neural activation patterns during retrieval and may further contribute to cognitive and behavioral flexibility through improved contextual processing within the default mode network (67–69). Importantly, both the retrosplenial cortex and DLPFC regions were identified only during the early phase of recall, when contextual information would be most relevant for cuing the memory representation.

It is important to note that although the study included an active control group, the unequal allocation ratio could limit our ability to detect effects in the control group owing to the low power associated with the sample size. Future studies are necessary to test whether the results persist with an equal randomization ratio. Other limitations include the small sample size for the skin conductance response analysis, owing to technical difficulties associated with assessing the electrodermal signal. Although we were able to replicate previous research findings (14) by demonstrating a positive association between extinction retention and hippocampal activation at baseline with a rather small sample, we lacked statistical power to detect improvements in extinction retention following mindfulness training using skin conductance responses. Future studies may utilize other metrics and/or criteria for computing an index of extinction retention (70). Additionally, the current sample included highly stressed but healthy individuals; future studies should investigate extinction recall following mindfulness training in patient populations and using personally relevant fear-inducing cues.

Impaired extinction recall has been implicated in the pathophysiology of several anxiety disorders (10,71,72). Successful retrieval of the extinction memory established during treatment is critical to the efficacy of exposure-based therapy (73,74). Previous investigations into the neural mechanisms associated with exposure therapy revealed experience-dependent neural adaptations in the hippocampus (75–77). Several other interventions, including treatment with cortisol (78), selective serotonin reuptake inhibitors (79), and psychotherapy (80), have been associated with alterations in the hippocampus as well. Accordingly, longitudinal changes in hippocampal structure and function have long been thought to be important for the development of stress resilience following mindfulness training (45). The current results, together with previously reported morphological differences between meditators and nonmeditators (18,19,41), suggest hippocampal-dependent changes in contextual retrieval as one plausible mechanism through which mindfulness-based interventions regulate affective response, foster stress resilience, curtail susceptibility to anxiety, and improve emotion regulation, while also advocating a novel way to enhance fear extinction.

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ARTICLE INFORMATION

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